(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 February 2003 (27.02.2003)

PCT

(10) International Publication Number
WO 03/015772 A1

(51) International Patent Classification[7]: A61K 31/425, A61P 25/00, 43/00

(21) International Application Number: PCT/EP02/07912

(22) International Filing Date: 17 July 2002 (17.07.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
01118838.0 13 August 2001 (13.08.2001) EP

(71) Applicant *(for all designated States except US)*: **MAX-PLANCK-GESELLSCHAFT ZUR FÖRDERUNG DER WISSENSCHAFTEN E.V.** [DE/DE]; Hofgartenstrasse 8, 80539 München (DE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BÖTTCHER, Henning** [DE/DE]; Stiftstrasse 12, 64287 Darmstadt (DE). **HERHAUS, Christian** [DE/DE]; Heidelberger Strasse 55b, 64625 Darmstadt (DE). **BARNICKEL, Gerhard** [DE/DE]; Emilstrasse 27, 64293 Darmstadt (DE). **WANKER, Erich, E.** [AT/DE]; Leichhardtstrasse 61, 14195 Berlin (DE). **HEISER, Volker** [DE/DE]; c/o Grohmann, Dresdner Str. 15, 10999 Berlin (DE). **LEHRACH, Hans** [DE/DE]; Terrassenstr. 31, 14129 Berlin (DE). **BROEKER, Wofgang** [DE/DE]; Marillenhof 2, 15831 Mahlow (DE). **DUNKEL, Ilona** [DE/DE]; Lützelsteiner Weg 52, 14195 Berlin (DE).

(74) Agent: **VOSSIUS & PARTNER**; Siebertstrasse 4, 81675 München (DE).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

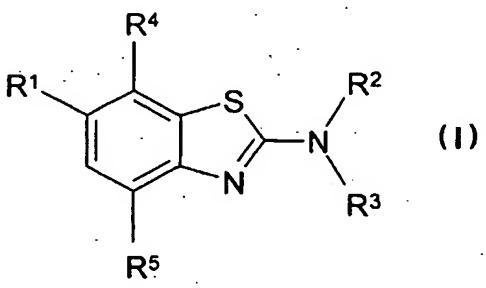
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/015772 A1

(54) Title: INHIBITORS OF POLYQ-AGGREGATION

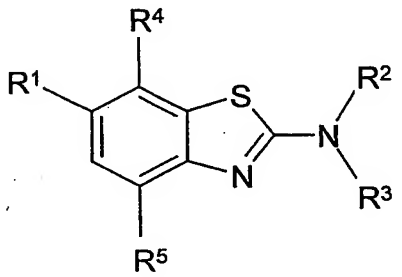


(I)

(57) Abstract: Compounds of formula I, wherein R^1, R^2, R3, R^4 and R^5 have the meanings as given in claim 1, and their pharmaceutically tolerable derivatives, solvates and stereoisomers and their use for the preparation of a pharmaceutical for inhibiting the formation of polyQ-aggregation.

Inhibitors of PolyQ-Aggregation

The invention relates to benzothiazole derivatives of formula I



I

wherein

R^1	is OH, OA or Hal
R^2, R^3	are independently of each other H or A,
R^2 and R^3	together are an alkylene chain with 4, 5 or 6 C atoms,
R^4, R^5	are independently of each other A or Hal,
A	is alkyl with 1, 2, 3, 4, 5 or 6 C atoms,
Hal	is F, Cl, Br or I,

and their pharmaceutically tolerable derivatives, solvates and stereoisomers,

with the proviso that the compounds

2-amino-6-hydroxy-4-methyl-benzothiazole,

2-dimethylamino-6-hydroxy-benzothiazole and

2-amino-4,7-dimethyl-6-hydroxy-benzothiazole are excluded.

Furthermore, the invention relates to the use of a compound of formula I and their pharmaceutically tolerable derivatives, solvates and stereoisomers for the preparation of a pharmaceutical for inhibiting the formation of polyQ-aggregation.

Preferably, the invention relates to compounds selected from the group consisting of

2-amino-7-chloro-6-hydroxy-4-methyl-benzothiazole,

2-amino-4-chloro-6-hydroxy-7-methyl-benzothiazole,

2-amino-5,7-dimethyl-6-hydroxy-benzothiazole,

6-methoxy-4,7-dimethyl-benzothiazol-2-ylamine,
N-(6-methoxy-4,7-dimethyl-benzothiazol-2-yl)-N-methylamine

and their pharmaceutically tolerable derivatives, solvates and stereoisomers.

Furthermore, the invention relates to the use of a compound selected from the group consisting of

2-amino-7-chloro-6-hydroxy-4-methyl-benzothiazole,
2-amino-4-chloro-6-hydroxy-7-methyl-benzothiazole,
2-amino-6-hydroxy-4-methyl-benzothiazole,
2-amino-5,7-dimethyl-6-hydroxy-benzothiazole,
2-dimethylamino-6-hydroxy-benzothiazole,
2-amino-4,7-dimethyl-6-hydroxy-benzothiazole,
6-methoxy-4,7-dimethyl-benzothiazol-2-ylamine,
N-(6-methoxy-4,7-dimethyl-benzothiazol-2-yl)-N-methylamine

and their pharmaceutically tolerable derivatives, solvates and stereoisomers for the preparation of a pharmaceutical for inhibiting the formation of polyQ-aggregation.

The invention was based on the object of finding compounds having valuable properties, in particular those which can be used for the production of medicaments.

Surprisingly, it has been found that above-mentioned compounds and their pharmaceutically tolerable derivatives, solvates and stereoisomers inhibit in vitro and in vivo formation of polyQ-aggregation. The accumulation of polyQ plays a direct role in the pathogenesis of neurodegenerative diseases (H.T.Orr, Development 15:925-932, 2001) such as Huntington's disease (V. Heiser et al., Proc. Natl. Acad. Sci. USA, 97, 6739-6744, 2000).

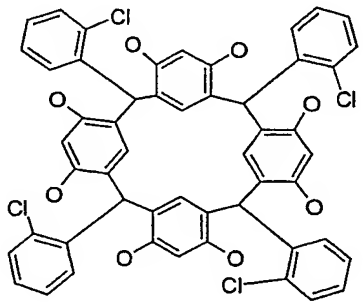
The compounds can be employed as pharmaceutical active compounds in human and veterinary medicine.

Other 2-amino-benzothiazole derivatives are described, for example, in EP 0 282 971 as cerebrovascular agents.

The following compounds are known:

2-amino-6-hydroxy-4-methyl-benzothiazole, synthesis is described by P.T.S. Lau and T.E. Gompf in J. Org. Chem. Vol. 35, 4103 - 4108;
2-dimethylamino-6-hydroxy-benzothiazole, CARN 943-04-4;
2-amino-4,7-dimethyl-6-hydroxy-benzothiazole, CARN 26278-83-1;
benzothiazole-2,5,6-triamine, CARN 313241-12-2;
[6,6']bibenzothiazolyl-2,2'-diamine, CARN 53357-04-3;
6,6'-thiodi(benzothiazole-2-amine), CARN 53357-07-6;
2,2'-*m*-phenylenedi(benzothiazole-6-amine), CARN 331653-50-0;
4-(6-methyl-benzooxazole-2-yl)-phenylamine, CARN 22501-77-5
2-(3-amino-phenyl)-quinoline-4-carboxylic acid, CARN 78660-91-0
2,7-dioxa-1,3,4,5,6,8,9,10-octaaza-dicyclopenta[*a,e*]cyclooctene, CARN 131122-64-0.

2,8,14,20-Tetrakis(2-chlorophenyl)-pentacyclo=[19.3.1.$1^{3,7}$.$1^{9,13}$,$1^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaen-4,6,10,12,16,18,22,24-octol =



Furthermore, the invention relates to the use of a compound of formula I and their pharmaceutically tolerable derivatives, solvates and stereoisomers for the preparation of a pharmaceutical for the treatment of Huntington's disease.

Preferably, the invention relates to the use of a compound selected from the group consisting of

2-amino-7-chloro-6-hydroxy-4-methyl-benzothiazole,
2-amino-4-chloro-6-hydroxy-7-methyl-benzothiazole,
2-amino-6-hydroxy-4-methyl-benzothiazole,
2-amino-5,7-dimethyl-6-hydroxy-benzothiazole,
2-dimethylamino-6-hydroxy-benzothiazole,
2-amino-4,7-dimethyl-6-hydroxy-benzothiazole,
6-methoxy-4,7-dimethyl-benzothiazol-2-ylamine,
N-(6-methoxy-4,7-dimethyl-benzothiazol-2-yl)-N-methylamine

and their pharmaceutically tolerable derivatives, solvates and stereoisomers for the preparation of a pharmaceutical for the treatment of Huntington's disease.

Moreover, the invention relates to the use of a compound of formula I and their pharmaceutically tolerable derivatives, solvates and stereoisomers for the preparation of a pharmaceutical for the treatment of spinal and bulbar muscular atrophy, dentatorubal pallidoluysian atrophy, spinocerebellar ataxia type-1, -2, -3, -6 and -7, Alzheimer's disease, bovine spongioform encephalopathy, primary systemic amyloidosis, secondary systemic amyloidosis, senile systemic amyloidosis, familial amyloid polyneuropathy I, hereditary cerebral amyloid angiopathy, hemodialysis-related amyloidosis, familial amyloid polyneuropathy III, Finnish hereditary systemic amyloidosis, type II diabetis, medullary carcinoma of thyroid, spongiform encephalopathies (prion diseases): Kuru, Gerstmann-Sträussler-Scheinker syndrome, familial insomnia, scrapie, atrial amyloidosis, hereditary non-neuropathic systemic amyloidosis, injection-localized amyloidosis, hereditary renal amyloidosis, amyotrophic lateral sclerosis, schizophrenia, sickle cell anaemia, unstable haemoglobin inclusion body haemolysis, α1-antitrypsin deficiency, antithrombin deficiency, thromboembolic disease and Parkinson's disease.

Moreover, the invention relates to the use of a compound selected from the group consisting of

2-amino-7-chloro-6-hydroxy-4-methyl-benzothiazole,
2-amino-4-chloro-6-hydroxy-7-methyl-benzothiazole,
2-amino-6-hydroxy-4-methyl-benzothiazole,
2-amino-5,7-dimethyl-6-hydroxy-benzothiazole,

2-dimethylamino-6-hydroxy-benzothiazole,
2-amino-4,7-dimethyl-6-hydroxy-benzothiazole,
6-methoxy-4,7-dimethyl-benzothiazol-2-ylamine,
N-(6-methoxy-4,7-dimethyl-benzothiazol-2-yl)-N-methylamine

and their pharmaceutically tolerable derivatives, solvates and stereoisomers for the preparation of a pharmaceutical for the treatment of spinal and bulbar muscular atrophy, dentatorubal pallidoluysian atrophy, spinocerebellar ataxia type-1, -2, -3, -6 and -7, Alzheimer's disease, bovine spongioform encephalopathy, primary systemic amyloidosis, secondary systemic amyloidosis, senile systemic amyloidosis, familial amyloid polyneuropathy I, hereditary cerebral amyloid angiopathy, hemodialysis-related amyloidosis, familial amyloid polyneuropathy III, Finnish hereditary systemic amyloidosis, type II diabetis, medullary carcinoma of thyroid, spongiform encephalopathies (prion diseases): Kuru, Gerstmann-Sträussler-Scheinker syndrome, familial insomnia, scrapie, atrial amyloidosis, hereditary non-neuropathic systemic amyloidosis, injection-localized amyloidosis, hereditary renal amyloidosis, amyotrophic lateral sclerosis, schizophrenia, sickle cell anaemia, unstable haemoglobin inclusion body haemolysis, α1-antitrypsin deficiency, antithrombin deficiency, thromboembolic disease and Parkinson's disease.

Furthermore, the invention relates to the use of a compound selected from the group consisting of

N-(6-phenylcarbamoyl-benzothiazole-2-yl)-terephthalamic acid methyl ester,
3-methoxy-*N*-[4-(6-methyl-benzothiazole-2-yl)-phenyl]-benzamide,
3-amino-*N*-[4-(6-methyl-2,3-dihydro-benzothiazole-2-yl)-phenyl]-benzamide,
4-[(4-benzothiazole-2-yl-phenylimino)-methyl]-2,6-dibromo-benzene-1,3-diol,
benzothiazole-2,5,6-triamine,
[6,6']bibenzothiazolyl-2,2'-diamine,
6,6'-thiodi(benzothiazole-2-amine),
2,2'-*m*-phenylenedi(benzothiazole-6-amine),

and their pharmaceutically tolerable derivatives, solvates and

stereoisomers for the preparation of a pharmaceutical for inhibiting the formation of polyQ-aggregation.

Furthermore, the invention relates to the use of a compound selected from the group consisting of

N-(6-phenylcarbamoyl-benzothiazole-2-yl)-terephthalamic acid methyl ester,
3-methoxy-*N*-[4-(6-methyl-benzothiazole-2-yl)-phenyl]-benzamide,
3-amino-*N*-[4-(6-methyl-2,3-dihydro-benzothiazole-2-yl)-phenyl]-benzamide,
4-[(4-benzothiazole-2-yl-phenylimino)-methyl]-2,6-dibromo-benzene-1,3-diol,
benzothiazole-2,5,6-triamine,
[6,6']bibenzothiazolyl-2,2'-diamine,
6,6'-thiodi(benzothiazole-2-amine),
2,2'-*m*-phenylenedi(benzothiazole-6-amine),

and their pharmaceutically tolerable derivatives, solvates and stereoisomers for the preparation of a pharmaceutical for the treatment of Huntington's disease.

Furthermore, the invention relates to compounds selected from the group consisting of
N-(6-phenylcarbamoyl-benzothiazol-2-yl)-terephthalamic acid methyl ester,
3-methoxy-*N*-[4-(6-methyl-benzothiazol-2-yl)-phenyl]-benzamide,
3-amino-*N*-[4-(6-methyl-2,3-dihydro-benzothiazol-2-yl)-phenyl]-benzamide,
4-[(4-benzothiazol-2-yl-phenylimino)-methyl]-2,6-dibromo-benzene-1,3-diol,

and their pharmaceutically tolerable derivatives, solvates and stereoisomers.

Moreover, the invention relates to compounds selected from the group consisting of

4-{3-[4-(5-methyl-[1,2,4]oxadiazole-3-yl)-phenyl]-2-oxo-oxazolidine-5-ylmethyl}-piperazine-1-carboxylic acid (3,4-dichloro-phenyl)-amide,
4-{3-[4-(5-methyl-[1,2,4]oxadiazole-3-yl)-phenyl]-2-oxo-oxazolidine-5-

ylmethyl}-piperazine-1-carboxylic acid (4-fluoro-3-nitro-phenyl)-amide, 4-{3-[4-(5-methyl-[1,2,4]oxadiazole-3-yl)-phenyl]-2-oxo-oxazolidine-5-ylmethyl}-piperazine-1-carboxylic acid (4-acetyl-phenyl)-amide, 1-{3-[4-(benzoylamino-imino-methyl)-phenyl]-2-oxo-oxazolidine-5-ylmethyl}-piperidine-4-carboxylic acid

and their pharmaceutically tolerable derivatives, solvates and stereoisomers.

Furthermore, the invention relates to the use of a compound selected from the group consisting of

4-{3-[4-(5-methyl-[1,2,4]oxadiazole-3-yl)-phenyl]-2-oxo-oxazolidine-5-ylmethyl}-piperazine-1-carboxylic acid (3,4-dichloro-phenyl)-amide, 4-{3-[4-(5-methyl-[1,2,4]oxadiazole-3-yl)-phenyl]-2-oxo-oxazolidine-5-ylmethyl}-piperazine-1-carboxylic acid (4-fluoro-3-nitro-phenyl)-amide, 4-{3-[4-(5-methyl-[1,2,4]oxadiazole-3-yl)-phenyl]-2-oxo-oxazolidine-5-ylmethyl}-piperazine-1-carboxylic acid (4-acetyl-phenyl)-amide, 1-{3-[4-(benzoylamino-imino-methyl)-phenyl]-2-oxo-oxazolidine-5-ylmethyl}-piperidine-4-carboxylic acid

and their pharmaceutically tolerable derivatives, solvates and stereoisomers for the preparation of a pharmaceutical for inhibiting the formation of polyQ-aggregation.

Furthermore, the invention relates to the use of a compound selected from the group consisting of

4-{3-[4-(5-methyl-[1,2,4]oxadiazole-3-yl)-phenyl]-2-oxo-oxazolidine-5-ylmethyl}-piperazine-1-carboxylic acid (3,4-dichloro-phenyl)-amide, 4-{3-[4-(5-methyl-[1,2,4]oxadiazole-3-yl)-phenyl]-2-oxo-oxazolidine-5-ylmethyl}-piperazine-1-carboxylic acid (4-fluoro-3-nitro-phenyl)-amide, 4-{3-[4-(5-methyl-[1,2,4]oxadiazole-3-yl)-phenyl]-2-oxo-oxazolidine-5-ylmethyl}-piperazine-1-carboxylic acid (4-acetyl-phenyl)-amide, 1-{3-[4-(benzoylamino-imino-methyl)-phenyl]-2-oxo-oxazolidine-5-ylmethyl}-piperidine-4-carboxylic acid

and their pharmaceutically tolerable derivatives, solvates and stereoisomers for the preparation of a pharmaceutical for the treatment of Huntington's disease.

Moreover, the invention relates to compounds selected from the group consisting of

5-[4-(thiazole-2-ylcarbamoyl)-phenyl]-furane-2-carboxylic acid thiazole-2-yl-amide,
8-methoxy-1-methyl-1,2,3,4-tetrahydro-benzo[4,5]imidazo-[1,2-*a*]pyrimidin-7-ylamine,
2,8,14,20-Tetrakis(2-chlorophenyl)-pentacyclo=[19.3.1.$1^{3,7}$.$1^{9,13}$,$1^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaen-4,6,10,12,16,18,22,24-octol,
5-[4-(2,4-dichloro-benzyloxy)-phenyl]-3*H*-[1,3,4]oxadiazole-2-thione

and their pharmaceutically tolerable derivatives, solvates and stereoisomers.

Furthermore, the invention relates to the use of a compound selected from the group consisting of

5-[4-(thiazole-2-ylcarbamoyl)-phenyl]-furane-2-carboxylic acid thiazole-2-yl-amide,
8-methoxy-1-methyl-1,2,3,4-tetrahydro-benzo[4,5]imidazo-[1,2-*a*]pyrimidin-7-ylamine,
2,8,14,20-Tetrakis(2-chlorophenyl)-pentacyclo=[19.3.1.$1^{3,7}$.$1^{9,13}$,$1^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaen-4,6,10,12,16,18,22,24-octol,
5-[4-(2,4-dichloro-benzyloxy)-phenyl]-3*H*-[1,3,4]oxadiazole-2-thione,
4-(6-methyl-benzooxazole-2-yl)-phenylamine,
2-(3-amino-phenyl)-quinoline-4-carboxylic acid,
2,7-dioxa-1,3,4,5,6,8,9,10-octaaza-dicyclopenta[*a*,*e*]cyclooctene

and their pharmaceutically tolerable derivatives, solvates and stereoisomers for the preparation of a pharmaceutical for inhibiting the formation of polyQ-aggregation.

Furthermore, the invention relates to the use of a compound selected from the group consisting of

5-[4-(thiazole-2-ylcarbamoyl)-phenyl]-furane-2-carboxylic acid thiazole-2-yl-amide,
8-methoxy-1-methyl-1,2,3,4-tetrahydro-benzo[4,5]imidazo-[1,2-*a*]pyrimidin-7-ylamine,
2,8,14,20-Tetrakis(2-chlorophenyl)-pentacyclo=[19.3.1.1^{3,7}.1^{9,13},1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaen-4,6,10,12,16,18,22,24-octol,
5-[4-(2,4-dichloro-benzyloxy)-phenyl]-3*H*-[1,3,4]oxadiazole-2-thione,
4-(6-methyl-benzooxazole-2-yl)-phenylamine,
2-(3-amino-phenyl)-quinoline-4-carboxylic acid,
2,7-dioxa-1,3,4,5,6,8,9,10-octaaza-dicyclopenta[*a,e*]cyclooctene

and their pharmaceutically tolerable derivatives, solvates and stereoisomers for the preparation of a pharmaceutical for the treatment of Huntington's disease.

The compounds mentioned-above are suitable as pharmaceutical active compounds for the treatment of Huntington's disease. They are furthermore suitable for the treatment of spinal and bulbar muscular atrophy, dentatorubal pallidoluysian atrophy, spinocerebellar ataxia type-1, -2, -3, -6 and -7, Alzheimer's disease, bovine spongioform encephalopathy, primary systemic amyloidosis, secondary systemic amyloidosis, senile systemic amyloidosis, familial amyloid polyneuropathy I, hereditary cerebral amyloid angiopathy, hemodialysis-related amyloidosis, familial amyloid polyneuropathy III, Finnish hereditary systemic amyloidosis, type II diabetis, medullary carcinoma of thyroid, spongiform encephalopathies (prion diseases): Kuru, Gerstmann- Sträussler-Scheinker syndrome, familial insomnia, scrapie, atrial amyloidosis, hereditary non-neuropathic systemic amyloidosis, injection-localized amyloidosis, hereditary renal amyloidosis, amyotrophic lateral sclerosis, schizophrenia, sickle cell

anaemia, unstable haemoglobin inclusion body haemolysis, α1-antitrypsin deficiency, antithrombin deficiency, thromboembolic disease and Parkinson's disease.

Finally they are suitable for the treatment of
Cystic fibrosis
Marfan syndrom
Amylotrophic lateral sclerosis
Scurvy
Maple syrup urine disease
Osteogenesis imperfecta
Cateracts
Familial hypercholesterolemia
α1-Antitrypsin deficiency
Tay-Sachs disease
Retinitis pigmentosa
Leprechaunism
Down's syndrome
Argyrophilic grain disease
Pick's disease
Corticobasal degeneration
Familial frontotemporal dementia
Non-Guamanian motor neurone disease
Niemann-Pick disease type C
Myotonic dystrophy
Hallervorden-Spatz disease.

For the identification of chemical compounds that prevent the formation of polyglutamine containing protein aggregates *in vitro* an automated filter retardation assay was developed. This assay is based on the finding that that polyglutamine-containing protein aggregates are insoluble in sodium dodecyl sulfate (SDS) and are retained on a cellulose acetate filter, whereas monomeric forms of the HD exon 1 protein with a polyglutamine sequence in the pathological range do not bind to the filter membrane.

The captured aggregates are then detected by simple immunoblot analysis using specific antibodies. The use of the filter retardation assay for the identification of chemical compounds that prevent the formation of huntingtin protein aggregates has been described (Scherzinger et al., 1997; Scherzinger et al., 1999; Wanker et al., 1999; Heiser et al., 2000; Wanker et al., 1998a; Wanker et al., 1998b).

For the evaluation of chemical compounds that have been identified by the high throughput screening a cell culture model system of HD has been developed. In this model system expression of HD exon 1 protein with a polyglutamine sequence in the pathological range (51 and 83 glutamines) is achieved through a tetracycline (tet)-regulated transactivator, a fusion protein consisting of the tet-repressor and a VP16 activation domain. This hybrid protein binds specifically to a tetracycline responsive DNA element TRE and promotes transcription from the adjacent CMV promoter. Tetracycine and its analogues such as doxycycline can bind to the transactivator and thereby prevent the hybrid protein from binding the TRE element. Thus, if doxycycline is present in the culture medium, transcription of mutant HD exon 1 protein is inhibited, while in its presence expression of HD exon 1 protein is induced. Formation and detection of SDS-insoluble huntingtin protein aggregates in this tetracycline-inducibe cell culture model system of HD has been described (Wälter et al., 2001).

Literature:

Heiser, V., Scherzinger, E., Boeddrich, A., Nordhoff, E., Lurz, R., Schugardt, N., Lehrach, H., and Wanker, E. E. (2000). Inhibition of huntingtin fibrillogenesis by specific antibodies and small molecules: Implications for Huntington's disease therapy, Proc Natl Acad Sci U S A 97, 6739-6744.

Scherzinger, E., Lurz, R., Turmaine, M., Mangiarini, L., Hollenbach, B., Hasenbank, R., Bates, G. P., Davies, S. W., Lehrach, H., and Wanker, E.

E. (1997). Huntingtin-encoded polyglutamine expansions form amyloid-like protein aggregates in vitro and in vivo, Cell *90*, 549-58.

Scherzinger, E., Sittler, A., Schweiger, K., Heiser, V., Lurz, R., Hasenbank, R., Bates, G. P., Lehrach, H., and Wanker, E. E. (1999). Self-assembly of polyglutamine-containing huntingtin fragments into amyloid-like fibrils: implications for Huntington's disease pathology, Proc Natl Acad Sci U S A *96*, 4604-9.

Wälter, S., Böddrich, A., Lurz, R., Scherzinger, E., Lüder, G., Lehrach, H., and Wanker, E. E. (2001). Accumulation of mutant huntingtin fragments in aggresome-like inclusion bodies as a result of insufficient protein degradation, Molecular Biology of the Cell, *in press*.

Wanker, E. E., Scherzinger, E., Bates, G. P., and Lehrach, H. (1998a). Novel composition and method for the detection of diseases associated with amylid-like fibril or protein aggregate formation. In PCT/EP98/04811.

Wanker, E. E., Scherzinger, E., Bates, G. P., and Lehrach, H. (1998b). Novel method of detecting amyloid-like fibrils or protein aggregates. In PCT/EP98/04810.

Wanker, E. E., Scherzinger, E., Heiser, V., Sittler, A., Eickhoff, H., and Lehrach, H. (1999). Membrane filter assay for detection of amyloid-like polyglutamine- containing protein aggregates, Methods Enzymol *309*, 375-86.

Hydrates and solvates are understood as meaning, for example, the hemi-, mono- or dihydrates, solvates are understood as meaning, for example, alcohol addition compounds such as, for example, with methanol or ethanol.

The term pharmaceutically tolerable derivatives is taken to mean, for example, the salts of the compounds according to the invention and also so-called prodrug compounds.

The term prodrug derivatives is taken to mean, for example, compounds of the formula I which have been modified with, for example, alkyl or acyl groups, sugars or oligopeptides and which are rapidly cleaved in the organism to give the effective compounds according to the invention.

These also include biodegradable polymer derivatives of the compounds according to the invention, as described, for example, in Int. J. Pharm. 115, 61-67 (1995).

The invention also relates to mixtures of the compounds of the formula I according to the invention, for example mixtures of two diastereomers, for example in the ratio 1:1, 1:2, 1:3, 1:4, 1:5, 1:10, 1:100 or 1:1000.
These are particularly preferably mixtures of stereoisomeric compounds.

For all radicals which occur more than once, such as, for example, A, their meanings are independent of one another.

A is alkyl, is unbranched (linear) or branched, and has 1, 2, 3, 4, 5 or 6 carbon atoms. A is preferably methyl, furthermore ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, furthermore also pentyl, 1-, 2- or 3-methylbutyl, 1,1- , 1,2- or 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, furthermore preferably, for example, trifluoromethyl, pentafluoroethyl or 1,1,1-trifluoroethyl.

The compounds of the present invention and also the starting substances for their preparation are otherwise prepared by methods known per se, such as are described in the literature (e.g. in the standard works such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), namely under reaction conditions which are known and suitable for the reactions mentioned. Use can also be made in this case of variants which are known per se, but not mentioned here in greater detail.

Synthesis of 2-amino-6-hydroxy-benzothiazoles is described by P.T.S. Lau and T.E. Gompf in J. Org. Chem. Vol. 35, 4103 - 4108.

It was found that under reactions conditions described in J. Org. Chem. (concentrated HCl) chlorinated side products are formed which can be separated from e.g. 2-amino-6-hydroxy-4-methyl-benzothiazole only with difficulties.

Surprisingly, by use of other strong acids like methanesulfonic acid, trifluoro acetic acid or formic acid, chlorination, or more generally halogenation if other halogen hydrogen acids are used, is avoided.

Benzothiazoles can also be prepared from anilines via thioureas (obtained according to C.R. Rasmussen Synthesis 1988,456 or Organic Synthesis, volume III, 735 (1955)) and subsequent treatment with sulfinylchloride according to the procedure of Th. Papenfuhs (Angewandte Chemie 94, 544 (1982).

Suitable inert solvents are, for example, hydrocarbons such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons such as trichloroethylene, 1,2-dichloroethane, carbon tetrachloride, chloroform or dichloromethane; alcohols such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF) or dioxane; glycol ethers such as ethylene glycol monomethyl or monoethyl ether (methyl glycol or ethyl glycol), ethylene glycol dimethyl ether (diglyme); ketones such as acetone or butanone; amides such as acetamide, dimethylacetamide, N-methylpyrrolidone (NMP) or dimethylformamide (DMF); nitriles such as acetonitrile; sulfoxides such as dimethyl sulfoxide (DMSO); carbon disulfide; carboxylic acids such as formic acid or acetic acid; nitro compounds such as nitromethane or nitrobenzene; esters such as ethyl acetate or mixtures of the solvents mentioned.

A base can be converted with an acid into the associated acid addition salt, for example by reaction of equivalent amounts of the base and of the acid in an inert solvent such as ethanol and subsequent evaporation. Suitable acids for this reaction are in particular those which yield physiologically acceptable salts. Thus inorganic acids can be used, e.g. sulfuric acid, nitric acid, halohydric acids such as hydrochloric acid or hydrobromic acid, phosphoric acids such as orthophosphoric acid, sulfamic acid, furthermore organic acids, in particular aliphatic, alicyclic, araliphatic, aromatic or heterocyclic mono- or polybasic carboxylic, sulfonic or sulfuric acids, e.g. formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane- or ethanesulfonic acid,

ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenemono- and -disulfonic acids and laurylsulfuric acid. Salts with physiologically unacceptable acids, e.g. picrates, can be used for the isolation and/or purification of the compounds of the formula I.

On the other hand, compounds can be converted into the corresponding metal salts, in particular alkali metal salts or alkaline earth metal salts, or into the corresponding ammonium salts using bases (e.g. sodium or potassium hydroxide or carbonate).
Physiologically acceptable organic bases, such as, for example, ethanolamine, can also be used.

The invention furthermore relates to the use of the compounds of the present invention and/or their physiologically acceptable salts for the production of pharmaceutical preparations, in particular by a non-chemical route. In this context, they can be brought into a suitable dose form together with at least one solid, liquid and/or semi-liquid vehicle or excipient and if appropriate in combination with one or more further active compounds.

The invention furthermore relates to pharmaceutical preparations comprising at least one compound of the formula I and/or one of its pharmaceutically tolerable derivatives, solvates and stereoisomers and optionally excipients and/or adjuvants.

The invention furthermore relates to pharmaceutical preparations comprising at least a compound selected from the group
2-amino-6-hydroxy-4,7-dimethyl-benzothiazole hydrochloride,
2-amino-6-hydroxy-4,7-dimethyl-benzothiazole methanesulfonate hydrate,
2-amino-7-chlor-6-hydroxy-4-methyl-benzothiazole,
6-methoxy-4,7-dimethyl-benzothiazol-2-ylamine or
N-(6-methoxy-4,7-dimethyl-benzothiazol-2-yl)-N-methylamine.

These preparations can be used as medicaments in human or veterinary medicine. Possible vehicles are organic or inorganic substances which are suitable for enteral (e.g. oral) or parenteral administration or topical application and do not react with the novel compounds, for example water,

vegetable oils, benzyl alcohols, alkylene glycols, polyethylene glycols, glycerol triacetate, gelatin, carbohydrates such as lactose or starch, magnesium stearate, talc and petroleum jelly. In particular, tablets, pills, coated tablets, capsules, powders, granules, syrups, juices or drops are used for oral administration, suppositories are used for rectal administration, solutions, preferably oily or aqueous solutions, furthermore suspensions, emulsions or implants, are used for parenteral administration and ointments, creams or powders are used for topical application, or transdermally in patches.

The novel compounds can also be lyophilized and the lyophilizates obtained can be used, for example, for the production of injection preparations. The preparations indicated can be sterilized and/or can contain excipients such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for influencing the osmotic pressure, buffer substances, colourants, flavourings and/or one or more further active compounds, e.g. one or more vitamins.

Pharmaceutical preparations which are suitable for administration in the form of aerosols or sprays are, for example, solutions, suspensions or emulsions of the active compound in a pharmaceutically acceptable solvent.

The compounds of the present invention and their physiologically acceptable salts and solvates can be used for the treatment and/or prophylaxis of the diseases or disease conditions indicated above.

In this context, the substances according to the invention are as a rule preferably administered in doses between approximately 0.1 and 100 mg, in particular between 1 and 10 mg, per dose unit. The daily dose is preferably between approximately 0.001 and 10 mg/kg of body weight. The specific dose for each patient, however, depends on all sorts of factors, for example on the efficacy of the specific compound employed, on the age, body weight, general state of health, sex, on the diet, on the time and route of administration, on the excretion rate, pharmaceutical combination and severity of the particular disorder to which the therapy applies. Oral administration is preferred.

Above and below, all temperatures are indicated in °C. In the following examples, "customary working up" means: if appropriate, water is added,

the mixture is adjusted, if necessary, depending on the constitution of the final product, to a pH of between 2 and 10 and extracted with ethyl acetate or dichloromethane, the organic phase is separated off, dried over sodium sulfate and evaporated, and the residue is purified by chromatography on silica gel and/or by crystallization.

Mass spectrometry (MS): EI (electron impact ionization) M^+
FAB (fast atom bombardment) $(M+H)^+$

Example 1

1.7 ml methanesulfonic acid is added to 1.4 g thiourea in 30 ml methanol. 5.0 g 2,5-dimethyl-1,4-benzochinon in 110 ml hot methanol is added and the mixture is stirred at room temperature for 5 days.
The mixture is filtered, the solvent is removed and the residue is washed with acetone.
5.3 g 2-amino-4,7-dimethyl-6-hydroxy-benzothiazole, methanesulfonate hydrate is obtained, m.p. 199-201°, from 2-chloro-5-methyl-1,4-benzochinon.

Example 2:
14 g 2-Methyl-5-chloroaniline is treated with ammonium isothiocyanate to obtain the N-(2-methyl-5-chlorophenyl)-thiourea that is subsequently treated with sulfinylchloride at 50 °C. The reaction is treated with excess water, stirred under heating for 30 min and filtered. The filtrate is treated with ammonia to reach pH 8. The product precipitated and is filtered off to yield 15 g 2-Amino-7-chloro-4-methylbenzothiazole mp. 206 °C.

Example 3:
1.5 g 2-amino-4,7-dimethyl-6-hydroxy-benzothiazole is dissolved in 20 ml acetonitril, 2 g potassium carbonate is added and at room temperature treated with 1.5 ml methyl iodide. After stirring at 40° for 3 hours, the reaction mixture is treted with water and extracted with ethyl acetate. The organic layer is separated, dried and evaporated. After chromatography with silica gel, 1.05 g 6-methoxy-4,7-dimethyl-benzothiazol-2-ylamine, m.p. 225-228°, and 50 mg N-(6-methoxy-4,7-dimethyl-benzothiazol-2-yl)-N-methylamine, m.p. 180-182° are isolated.

Pharmacological Tests

Testsystems:

In vitro: Proteolytic cleavage of GST-Huntington fusion-protein. Quantification of the precipitated aggregates after 18 h (filter retardation assay, Protein conc. ca. 0.65 μM).

In vivo: Incubation of the stable cell-line Tet-off (10 μM, 72 h). Lysates are used for quantification of aggregates and determination of the overall protein amount.

The following compounds

2-amino-4-methyl-6-hydroxy-benzimidazole (EMD 59966),
2-amino-4,7-dimethyl-6-hydroxy-benzimidazole methanesulfonate hydrate (EMD 393607),
2-amino-4,7-dimethyl-6-hydroxy-benzimidazole hydrochloride (EMD 391979),

have been tested in comparison to 2-amino-4-methyl-benzimidazole (EMD 390908), which is known from EP 282971.

Compounds (EMD 59966), (EMD 393607) and (EMD 391979) show a significant decrease of the formation of polyQ-aggregation (Fig. 1).

The following examples relate to pharmaceutical preparations:

Example A: Injection vials

A solution of 100 g of 2-amino-6-hydroxy-4,7-dimethyl-benzothiazole hydrochloride, 2-amino-6-hydroxy-4,7-dimethyl-benzothiazole methanesulfonate hydrate or 2-amino-7-chlor-6-hydroxy-4-methyl-benzothiazole and 5 g of disodium hydrogenphosphate is adjusted to pH 6.5 using 2N hydrochloric acid in 3 l of double-distilled water, sterile filtered, dispensed into injection vials, lyophilized under sterile conditions and aseptically sealed. Each injection vial contains 5 mg of active compound.

Example B: Suppositories

A mixture of 20 g of 2-amino-6-hydroxy-4,7-dimethyl-benzothiazole hydrochloride, 2-amino-6-hydroxy-4,7-dimethyl-benzothiazole methanesulfonate hydrate or 2-amino-7-chlor-6-hydroxy-4-methyl-benzothiazole is fused with 100 g of soya lecithin and 1400 g of cocoa butter, poured into moulds and allowed to cool. Each suppository contains 20 mg of active compound.

Example C: Solution

A solution is prepared from 1 g 2-amino-6-hydroxy-4,7-dimethyl-benzothiazole hydrochloride, 2-amino-6-hydroxy-4,7-dimethyl-benzothiazole methanesulfonate hydrate or 2-amino-7-chlor-6-hydroxy-4-methyl-benzothiazole, 9.38 g of $NaH_2PO_4 \cdot 2\ H_2O$, 28.48 g of $Na_2HPO_4 \cdot 12\ H_2O$ and 0.1 g of benzalkonium chloride in 940 ml of doubled-distilled water. It is adjusted to pH 6.8, made up to 1 l and sterilized by irradiation. This solution can be used in the form of eye drops.

Example D: Ointment

500 mg of 2-amino-6-hydroxy-4,7-dimethyl-benzothiazole hydrochloride, 2-amino-6-hydroxy-4,7-dimethyl-benzothiazole methanesulfonate hydrate or 2-amino-7-chlor-6-hydroxy-4-methyl-benzothiazole are mixed with 99.5 g

of petroleum jelly under aseptic conditions.

Example E: Tablets

A mixture of 1 kg of 2-amino-6-hydroxy-4,7-dimethyl-benzothiazole hydrochloride, 2-amino-6-hydroxy-4,7-dimethyl-benzothiazole methanesulfonate hydrate or 2-amino-7-chlor-6-hydroxy-4-methyl-benzothiazole, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is compressed in a customary manner to give tablets such that each tablet contains 10 mg of active compound.

Example F: Coated tablets

Tablets are pressed analogously to Example E and then coated in a customary manner with a coating of sucrose, potato starch, talc, tragacanth and colourant.

Example G: Capsules

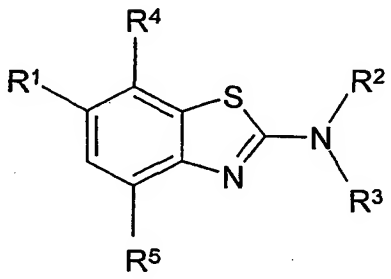
2 kg of 2-amino-6-hydroxy-4,7-dimethyl-benzothiazole hydrochloride, 2-amino-6-hydroxy-4,7-dimethyl-benzothiazole methanesulfonate hydrate or 2-amino-7-chlor-6-hydroxy-4-methyl-benzothiazole are filled into hard gelatin capsules in a customary manner such that each capsule contains 20 mg of the active compound.

Example H: Ampoules

A solution of 2-amino-6-hydroxy-4,7-dimethyl-benzothiazole hydrochloride, 2-amino-6-hydroxy-4,7-dimethyl-benzothiazole methanesulfonate hydrate or 2-amino-7-chlor-6-hydroxy-4-methyl-benzothiazole in 60 l of double-distilled water is sterile filtered, dispensed into ampoules, lyophilized under sterile conditions and aseptically sealed. Each ampoule contains 10 mg of active compound.

Patent Claims

1. Benzothiazole derivatives of formula I



I

wherein

R^1 is OH, OA or Hal

R^2, R^3 are independently of each other H or A,

R^2 and R^3 together are an alkylene chain with 4, 5 or 6 C atoms,

R^4, R^5 are independently of each other A or Hal,

A is alkyl with 1, 2, 3, 4, 5 or 6 C atoms,

Hal is F, Cl, Br or I,

and their pharmaceutically tolerable derivatives, solvates and stereoisomers,

with the proviso that the compounds

2-amino-6-hydroxy-4-methyl-benzothiazole,

2-dimethylamino-6-hydroxy-benzothiazole and

2-amino-4,7-dimethyl-6-hydroxy-benzothiazole are excluded.

2. Benzothiazole derivatives according to claim 1 selected from the group

2-amino-7-chloro-6-hydroxy-4-methyl-benzothiazole,
2-amino-4-chloro-6-hydroxy-7-methyl-benzothiazole,
2-amino-5,7-dimethyl-6-hydroxy-benzothiazole,
6-methoxy-4,7-dimethyl-benzothiazol-2-ylamine,
N-(6-methoxy-4,7-dimethyl-benzothiazol-2-yl)-N-methylamine

and their pharmaceutically tolerable derivatives, solvates and stereoisomers.

3. The compound 2-amino-4,7-dimethyl-6-hydroxy-benzothiazole, methanesulfonate hydrate.

4. Pharmaceutical preparation comprising at least one compound of the formula I and/or one of its pharmaceutically tolerable derivatives, solvates and stereoisomers and optionally excipients and/or adjuvants.

5. Pharmaceutical preparation according to claim 4 comprising at least one compound selected from the group
2-amino-6-hydroxy-4,7-dimethyl-benzothiazole hydrochloride,
2-amino-6-hydroxy-4,7-dimethyl-benzothiazole methanesulfonate hydrate,
2-amino-7-chlor-6-hydroxy-4-methyl-benzothiazole,
6-methoxy-4,7-dimethyl-benzothiazol-2-ylamine or
N-(6-methoxy-4,7-dimethyl-benzothiazol-2-yl)-N-methylamine.

6. Use of a compound of formula I
and their pharmaceutically tolerable derivatives, solvates and stereoisomers for the preparation of a pharmaceutical for inhibiting the formation of polyQ-aggregation.

7. Use according to claim 6 of a compound selected from the group consisting of

2-amino-7-chloro-6-hydroxy-4-methyl-benzothiazole,
2-amino-4-chloro-6-hydroxy-7-methyl-benzothiazole,
2-amino-6-hydroxy-4-methyl-benzothiazole,
2-amino-5,7-dimethyl-6-hydroxy-benzothiazole,
2-dimethylamino-6-hydroxy-benzothiazole,
2-amino-4,7-dimethyl-6-hydroxy-benzothiazole,
6-methoxy-4,7-dimethyl-benzothiazol-2-ylamine,
N-(6-methoxy-4,7-dimethyl-benzothiazol-2-yl)-N-methylamine

and their pharmaceutically tolerable derivatives, solvates and stereoisomers for the preparation of a pharmaceutical for inhibiting the formation of polyQ-aggregation.

8. Use of a compound of formula I
and their pharmaceutically tolerable derivatives, solvates and stereoisomers for the preparation of a pharmaceutical for the treatment of Huntington's disease.

9. Use according to claim 8 of a compound selected from the group consisting of

2-amino-7-chloro-6-hydroxy-4-methyl-benzothiazole,
2-amino-4-chloro-6-hydroxy-7-methyl-benzothiazole,
2-amino-6-hydroxy-4-methyl-benzothiazole,
2-amino-5,7-dimethyl-6-hydroxy-benzothiazole,
2-dimethylamino-6-hydroxy-benzothiazole,
2-amino-4,7-dimethyl-6-hydroxy-benzothiazole,
6-methoxy-4,7-dimethyl-benzothiazol-2-ylamine,
N-(6-methoxy-4,7-dimethyl-benzothiazol-2-yl)-N-methylamine

and their pharmaceutically tolerable derivatives, solvates and stereoisomers for the preparation of a pharmaceutical for the treatment of Huntington's disease.

10. Use of a compound of formula I
and their pharmaceutically tolerable derivatives, solvates and stereoisomers for the preparation of a pharmaceutical for the treatment of spinal and bulbar muscular atrophy, dentatorubal pallidoluysian atrophy, spinocerebellar ataxia type-1, -2, -3, -6 and -7, Alzheimer's disease, bovine spongioform encephalopathy, primary systemic amyloidosis, secondary systemic amyloidosis, senile systemic amyloidosis, familial amyloid polyneuropathy I, hereditary cerebral amyloid angiopathy, hemodialysis-related amyloidosis, familial amyloid polyneuropathy III, Finnish hereditary systemic amyloidosis, type II diabetis, medullary carcinoma of thyroid, spongiform encephalopathies (prion diseases): Kuru, Gerstmann- Sträussler-Scheinker syndrome, familial insomnia,

scrapie, atrial amyloidosis, hereditary non-neuropathic systemic amyloidosis, injection-localized amyloidosis, hereditary renal amyloidosis, amyotrophic lateral sclerosis, schizophrenia, sickle cell anaemia, unstable haemoglobin inclusion body haemolysis, α1-antitrypsin deficiency, antithrombin deficiency, thromboembolic disease and Parkinson's disease.

11. Compounds selected from the group consisting of

N-(6-phenylcarbamoyl-benzothiazol-2-yl)-terephthalamic acid methyl ester,
3-methoxy-*N*-[4-(6-methyl-benzothiazol-2-yl)-phenyl]-benzamide,
3-amino-*N*-[4-(6-methyl-2,3-dihydro-benzothiazol-2-yl)-phenyl]-benzamide,
4-[(4-benzothiazol-2-yl-phenylimino)-methyl]-2,6-dibromo-benzene-1,3-diol,

and their pharmaceutically tolerable derivatives, solvates and stereoisomers.

12. Use of a compound selected from the group consisting of

N-(6-phenylcarbamoyl-benzothiazole-2-yl)-terephthalamic acid methyl ester,
3-methoxy-*N*-[4-(6-methyl-benzothiazole-2-yl)-phenyl]-benzamide,
3-amino-*N*-[4-(6-methyl-2,3-dihydro-benzothiazole-2-yl)-phenyl]-benzamide,
4-[(4-benzothiazole-2-yl-phenylimino)-methyl]-2,6-dibromo-benzene-1,3-diol,
benzothiazole-2,5,6-triamine,
[6,6']bibenzothiazolyl-2,2'-diamine,
6,6'-thiodi(benzothiazole-2-amine),
2,2'-*m*-phenylenedi(benzothiazole-6-amine),

and their pharmaceutically tolerable derivatives, solvates and stereoisomers for the preparation of a pharmaceutical for inhibiting the formation of polyQ-aggregation.

13. Use of a compound selected from the group consisting of

N-(6-phenylcarbamoyl-benzothiazole-2-yl)-terephthalamic acid methyl ester,
3-methoxy-*N*-[4-(6-methyl-benzothiazole-2-yl)-phenyl]-benzamide,
3-amino-*N*-[4-(6-methyl-2,3-dihydro-benzothiazole-2-yl)-phenyl]-benzamide,
4-[(4-benzothiazole-2-yl-phenylimino)-methyl]-2,6-dibromo-benzene-1,3-diol,
benzothiazole-2,5,6-triamine,
[6,6']bibenzothiazolyl-2,2'-diamine,
6,6'-thiodi(benzothiazole-2-amine),
2,2'-*m*-phenylenedi(benzothiazole-6-amine),

and their pharmaceutically tolerable derivatives, solvates and stereoisomers for the preparation of a pharmaceutical for the treatment of Huntington's disease.

14. Compounds selected from the group consisting of

4-{3-[4-(5-methyl-[1,2,4]oxadiazole-3-yl)-phenyl]-2-oxo-oxazolidine-5-ylmethyl}-piperazine-1-carboxylic acid (3,4-dichloro-phenyl)-amide,
4-{3-[4-(5-methyl-[1,2,4]oxadiazole-3-yl)-phenyl]-2-oxo-oxazolidine-5-ylmethyl}-piperazine-1-carboxylic acid (4-fluoro-3-nitro-phenyl)-amide,
4-{3-[4-(5-methyl-[1,2,4]oxadiazole-3-yl)-phenyl]-2-oxo-oxazolidine-5-ylmethyl}-piperazine-1-carboxylic acid (4-acetyl-phenyl)-amide,
1-{3-[4-(benzoylamino-imino-methyl)-phenyl]-2-oxo-oxazolidine-5-ylmethyl}-piperidine-4-carboxylic acid

and their pharmaceutically tolerable derivatives, solvates and stereoisomers.

15. Use of a compound selected from the group consisting of

4-{3-[4-(5-methyl-[1,2,4]oxadiazole-3-yl)-phenyl]-2-oxo-oxazolidine-5-ylmethyl}-piperazine-1-carboxylic acid (3,4-dichloro-phenyl)-

amide,
4-{3-[4-(5-methyl-[1,2,4]oxadiazole-3-yl)-phenyl]-2-oxo-oxazolidine-5-ylmethyl}-piperazine-1-carboxylic acid (4-fluoro-3-nitro-phenyl)-amide,
4-{3-[4-(5-methyl-[1,2,4]oxadiazole-3-yl)-phenyl]-2-oxo-oxazolidine-5-ylmethyl}-piperazine-1-carboxylic acid (4-acetyl-phenyl)-amide,
1-{3-[4-(benzoylamino-imino-methyl)-phenyl]-2-oxo-oxazolidine-5-ylmethyl}-piperidine-4-carboxylic acid

and their pharmaceutically tolerable derivatives, solvates and stereoisomers for the preparation of a pharmaceutical for inhibiting the formation of polyQ-aggregation.

16. Use of a compound selected from the group consisting of

4-{3-[4-(5-methyl-[1,2,4]oxadiazole-3-yl)-phenyl]-2-oxo-oxazolidine-5-ylmethyl}-piperazine-1-carboxylic acid (3,4-dichloro-phenyl)-amide,
4-{3-[4-(5-methyl-[1,2,4]oxadiazole-3-yl)-phenyl]-2-oxo-oxazolidine-5-ylmethyl}-piperazine-1-carboxylic acid (4-fluoro-3-nitro-phenyl)-amide,
4-{3-[4-(5-methyl-[1,2,4]oxadiazole-3-yl)-phenyl]-2-oxo-oxazolidine-5-ylmethyl}-piperazine-1-carboxylic acid (4-acetyl-phenyl)-amide,
1-{3-[4-(benzoylamino-imino-methyl)-phenyl]-2-oxo-oxazolidine-5-ylmethyl}-piperidine-4-carboxylic acid

and their pharmaceutically tolerable derivatives, solvates and stereoisomers for the preparation of a pharmaceutical for the treatment of Huntington's disease.

17. Compounds selected from the group consisting of

5-[4-(thiazole-2-ylcarbamoyl)-phenyl]-furane-2-carboxylic acid thiazole-2-yl-amide,
8-methoxy-1-methyl-1,2,3,4-tetrahydro-benzo[4,5]imidazo-[1,2-*a*]pyrimidin-7-ylamine,
2,8,14,20-Tetrakis(2-chlorophenyl)-pentacyclo=[19.3.1.$1^{3,7}$.$1^{9,13}$,$1^{15,19}$]octacosa-

1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaen-4,6,10,12,16,18,22,24-octol,
5-[4-(2,4-dichloro-benzyloxy)-phenyl]-3*H*-[1,3,4]oxadiazole-2-thione

and their pharmaceutically tolerable derivatives, solvates and stereoisomers.

18. Use of a compound selected from the group consisting of

5-[4-(thiazole-2-ylcarbamoyl)-phenyl]-furane-2-carboxylic acid thiazole-2-yl-amide,
8-methoxy-1-methyl-1,2,3,4-tetrahydro-benzo[4,5]imidazo-[1,2-*a*]pyrimidin-7-ylamine,
2,8,14,20-Tetrakis(2-chlorophenyl)-pentacyclo=[19.3.1.1^{3,7}.1^{9,13},1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaen-4,6,10,12,16,18,22,24-octol,
5-[4-(2,4-dichloro-benzyloxy)-phenyl]-3*H*-[1,3,4]oxadiazole-2-thione,
4-(6-methyl-benzooxazole-2-yl)-phenylamine,
2-(3-amino-phenyl)-quinoline-4-carboxylic acid,
2,7-dioxa-1,3,4,5,6,8,9,10-octaaza-dicyclopenta[*a,e*]cyclooctene

and their pharmaceutically tolerable derivatives, solvates and stereoisomers for the preparation of a pharmaceutical for inhibiting the formation of polyQ-aggregation.

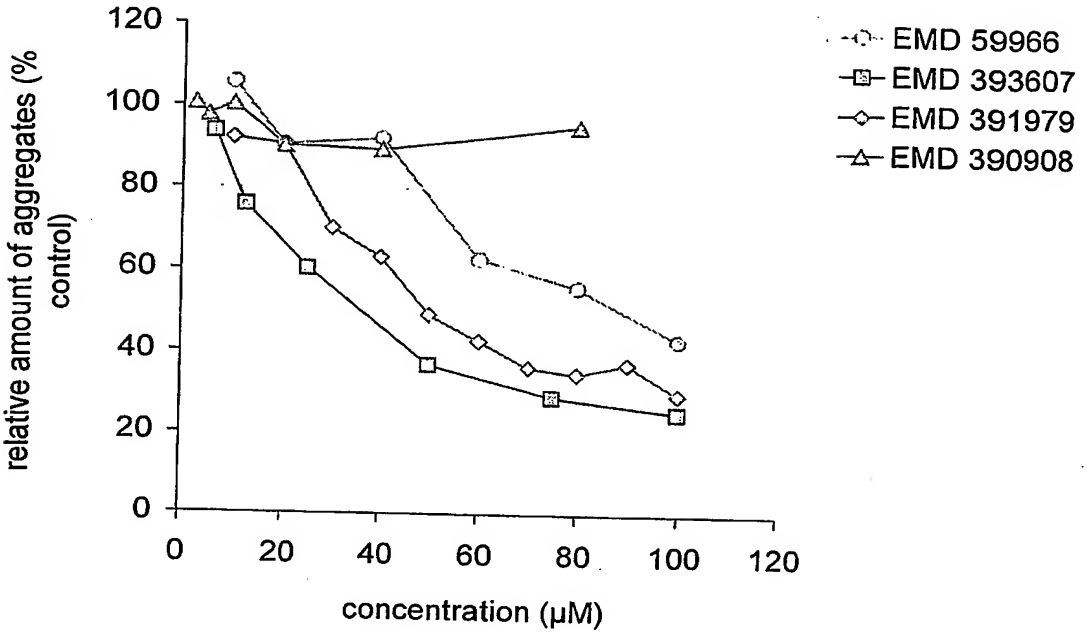
19. Use of a compound selected from the group consisting of

5-[4-(thiazole-2-ylcarbamoyl)-phenyl]-furane-2-carboxylic acid thiazole-2-yl-amide,
8-methoxy-1-methyl-1,2,3,4-tetrahydro-benzo[4,5]imidazo-[1,2-*a*]pyrimidin-7-ylamine,
2,8,14,20-Tetrakis(2-chlorophenyl)-pentacyclo=[19.3.1.1^{3,7}.1^{9,13},1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaen-4,6,10,12,16,18,22,24-octol,
5-[4-(2,4-dichloro-benzyloxy)-phenyl]-3*H*-[1,3,4]oxadiazole-2-thione,
4-(6-methyl-benzooxazole-2-yl)-phenylamine,

2-(3-amino-phenyl)-quinoline-4-carboxylic acid,
2,7-dioxa-1,3,4,5,6,8,9,10-octaaza-dicyclopenta[*a,e*]cyclooctene

and their pharmaceutically tolerable derivatives, solvates and stereoisomers for the preparation of a pharmaceutical for the treatment of Huntington's disease.

Fig.1


relative amount of aggregates (% control)
120
100
80
60
40
20
0
0
20
40
60
80
100
120
concentration (µM)
EMD 59966
EMD 393607
EMD 391979
EMD 390908

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/07912

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/425 A61P25/00 A61P43/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, EMBASE, MEDLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 282 971 A (WARNER LAMBERT CO) 21 September 1988 (1988-09-21) cited in the application abstract page 2, line 21 -page 4, line 31 claims 1-6	1-10
A	---	11-13
X	EP 0 507 318 A (EISAI CO LTD) 7 October 1992 (1992-10-07) abstract page 3, line 35 -page 4, line 43 example 6 claims 1-41	1-10
A	---	11-13
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 December 2002	27.01.03

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Taylor, G.M.

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 65516 A (KARPUJ MARCELLA V ;YEDA RES & DEV (IL); STEINMAN LAWRENCE (US)) 23 December 1999 (1999-12-23) abstract page 7, line 10 - line 15 page 9, line 32 -page 11, line 34 claims 1-3	1-10
A		11-13
X	EP 0 374 041 A (RHONE POULENC SANTE) 20 June 1990 (1990-06-20) abstract page 2, line 1 - line 29 examples 1-17 claims 1-8	1-10
A		11-13
X	US 5 795 903 A (LOUVEL ERIK ET AL) 18 August 1998 (1998-08-18) abstract column 1, line 7 - line 30 claims 1-9	1-10
A		11-13
A	EP 0 855 391 A (SNOW BRAND MILK PROD CO LTD) 29 July 1998 (1998-07-29) abstract examples 100,101	11-13
A	WO 00 73282 A (SMITHKLINE BEECHAM CORP ;WIDDOWSON KATHERINE L (US); PALOVICH MICH) 7 December 2000 (2000-12-07) abstract claim 11 Figure 1, compound 412	11-13
A	US 5 348 969 A (ROMINE JEFFREY L ET AL) 20 September 1994 (1994-09-20) abstract	14-19
A	PEREIRA, E R, ET AL.: "Syntheses and antimicrobial activities of five-membered ring heterocycles coupled to indole moieties" JOURNAL OF ANTIBIOTICS, vol. 49, no. 4, 1996, pages 380-385, XP009003375 the whole document	14-19

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/07912

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0282971 A	21-09-1988	US 4826860 A	02-05-1989
		AT 116134 T	15-01-1995
		CA 1312287 A1	05-01-1993
		DE 3852555 D1	09-02-1995
		DE 3852555 T2	04-05-1995
		EP 0282971 A2	21-09-1988
		ES 2065895 T3	01-03-1995
		GR 3015466 T3	30-06-1995
		JP 2602275 B2	23-04-1997
		JP 63313729 A	21-12-1988
		US 4918090 A	17-04-1990
EP 0507318 A	07-10-1992	AT 157976 T	15-09-1997
		AU 658868 B2	04-05-1995
		AU 1399092 A	08-10-1992
		CA 2064992 A1	05-10-1992
		CN 1065457 A ,B	21-10-1992
		DE 69222076 D1	16-10-1997
		DE 69222076 T2	19-02-1998
		DK 507318 T3	23-03-1998
		EP 0507318 A1	07-10-1992
		ES 2104761 T3	16-10-1997
		FI 921303 A	05-10-1992
		GR 3024867 T3	30-01-1998
		HU 62890 A2	28-06-1993
		IE 920921 A1	07-10-1992
		JP 2848998 B2	20-01-1999
		JP 5178855 A	20-07-1993
		KR 9700954 B1	21-01-1997
		MX 9201544 A1	01-10-1992
		NO 921282 A	05-10-1992
		NZ 242204 A	24-02-1995
		PH 30229 A	05-02-1997
		RU 2041216 C1	09-08-1995
		US 5420144 A	30-05-1995
		US 5635519 A	03-06-1997
		US 5300518 A	05-04-1994
WO 9965516 A	23-12-1999	AU 4823999 A	05-01-2000
		WO 9965516 A1	23-12-1999
EP 0374041 A	20-06-1990	FR 2640624 A1	22-06-1990
		FR 2649705 A2	18-01-1991
		AT 77375 T	15-07-1992
		CA 2005592 A1	15-06-1990
		DE 68901859 D1	23-07-1992
		DE 68901859 T2	14-01-1993
		DK 633489 A	16-06-1990
		EP 0374041 A1	20-06-1990
		ES 2043070 T3	16-12-1993
		FI 93108 B	15-11-1994
		GR 3004937 T3	28-04-1993
		IE 64657 B1	23-08-1995
		JP 2013895 C	02-02-1996
		JP 2223571 A	05-09-1990
		JP 7049425 B	31-05-1995
		NO 895032 A ,B,	18-06-1990
		PT 92606 A ,B	29-06-1990

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/07912

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 11-19
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 11-19

In view of the large number of independent claims (15 out of 19 are independent) presently on file, which render it difficult, if not impossible, to determine the matter for which protection is sought, the present application fails to comply with the clarity and conciseness requirements of Art. 6 PCT (see also Rule 6.1(a) PCT) to such an extent that a meaningful search over the whole subject-matter is impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and concise), namely claims 1-10, as well as the medical uses of benzothiazoles (claims 11-13) and oxazolidinones (claims 14-19).

Furthermore, the definition of a disease in terms of its mechanism of action is not regarded as being clear (Art. 6 PCT). The search will therefore be further restricted to those diseases actually mentions (claims 8 and 10).

Additionally, it should be noted that claims 11-19 are not clear because they are not supported by the description (Art. 5 and 6 PCT). There is no disclosure of how the claimed compounds are prepared, and thus the claims lack an enabling disclosure.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-10

   Benzothiazole derivatives of Formula I and their use in inhibiting polyQ aggregation.

2. Claims: 11-13

   Benzothiazole derivatives of not falling within Formula I and their use in inhibiting polyQ aggregation.

3. Claims: 14-19

   Numerous compounds, not containing the benzothiazole nucleus, for inhibiting polyQ aggregation.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/07912

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP 0282971 A	21-09-1988	US	4826860 A	02-05-1989
		AT	116134 T	15-01-1995
		CA	1312287 A1	05-01-1993
		DE	3852555 D1	09-02-1995
		DE	3852555 T2	04-05-1995
		EP	0282971 A2	21-09-1988
		ES	2065895 T3	01-03-1995
		GR	3015466 T3	30-06-1995
		JP	2602275 B2	23-04-1997
		JP	63313729 A	21-12-1988
		US	4918090 A	17-04-1990
EP 0507318 A	07-10-1992	AT	157976 T	15-09-1997
		AU	658868 B2	04-05-1995
		AU	1399092 A	08-10-1992
		CA	2064992 A1	05-10-1992
		CN	1065457 A ,B	21-10-1992
		DE	69222076 D1	16-10-1997
		DE	69222076 T2	19-02-1998
		DK	507318 T3	23-03-1998
		EP	0507318 A1	07-10-1992
		ES	2104761 T3	16-10-1997
		FI	921303 A	05-10-1992
		GR	3024867 T3	30-01-1998
		HU	62890 A2	28-06-1993
		IE	920921 A1	07-10-1992
		JP	2848998 B2	20-01-1999
		JP	5178855 A	20-07-1993
		KR	9700954 B1	21-01-1997
		MX	9201544 A1	01-10-1992
		NO	921282 A	05-10-1992
		NZ	242204 A	24-02-1995
		PH	30229 A	05-02-1997
		RU	2041216 C1	09-08-1995
		US	5420144 A	30-05-1995
		US	5635519 A	03-06-1997
		US	5300518 A	05-04-1994
WO 9965516 A	23-12-1999	AU	4823999 A	05-01-2000
		WO	9965516 A1	23-12-1999
EP 0374041 A	20-06-1990	FR	2640624 A1	22-06-1990
		FR	2649705 A2	18-01-1991
		AT	77375 T	15-07-1992
		CA	2005592 A1	15-06-1990
		DE	68901859 D1	23-07-1992
		DE	68901859 T2	14-01-1993
		DK	633489 A	16-06-1990
		EP	0374041 A1	20-06-1990
		ES	2043070 T3	16-12-1993
		FI	93108 B	15-11-1994
		GR	3004937 T3	28-04-1993
		IE	64657 B1	23-08-1995
		JP	2013895 C	02-02-1996
		JP	2223571 A	05-09-1990
		JP	7049425 B	31-05-1995
		NO	895032 A ,B,	18-06-1990
		PT	92606 A ,B	29-06-1990

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/07912

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0374041 A		US 5236940 A	17-08-1993
US 5795903 A	18-08-1998	FR 2726271 A1	03-05-1996
		AT 187169 T	15-12-1999
		AU 3809095 A	23-05-1996
		DE 69513679 D1	05-01-2000
		DE 69513679 T2	21-06-2000
		DK 788491 T3	08-05-2000
		EP 0788491 A1	13-08-1997
		ES 2139247 T3	01-02-2000
		WO 9613492 A1	09-05-1996
		GR 3032022 T3	31-03-2000
		JP 10508014 T	04-08-1998
		ZA 9508861 A	09-05-1996
EP 0855391 A	29-07-1998	JP 3243733 B2	07-01-2002
		JP 10101650 A	21-04-1998
		AU 734322 B2	07-06-2001
		AU 3784197 A	25-02-1998
		EP 0855391 A1	29-07-1998
		NZ 330117 A	28-10-1999
		US 5959107 A	28-09-1999
		CA 2234051 A1	12-02-1998
		WO 9805648 A1	12-02-1998
WO 0073282 A	07-12-2000	AU 5168900 A	18-12-2000
		WO 0073282 A1	07-12-2000
US 5348969 A	20-09-1994	NONE	